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Better Outcome After Pediatric Defibrillation Dosage Than Adult Dosage in a Swine Model of Pediatric Ventricular Fibrillation

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OBJECTIVES This study was designed to compare outcome after adult defibrillation dosing versus pediatric dosing in a piglet model of prolonged prehospital ventricular fibrillation (VF).

BACKGROUND Weight-based 2 to 4 J/kg monophasic defibrillation dosing is recommended for children in VF, but impractical for automated external defibrillator (AED) use. Present AEDs can only provide adult shock doses or newly developed attenuated adult doses intended for children. A single escalating energy sequence (50/75/86 J) of attenuated adult-dose biphasic shocks (pediatric dosing) is at least as effective as escalating monophasic weight-based dosing for prolonged VF in piglets, but this approach has not been compared to standard adult biphasic dosing.

METHODS Following 7 min of untreated VF, piglets weighing 13 to 26 kg (19 ± 1 kg) received either biphasic 50/75/86 J (pediatric dose) or biphasic 200/300/360 J (adult dose) therapies during simulated prehospital life support.

RESULTS Return of spontaneous circulation was attained in 15 of 16 pediatric-dose piglets and 14 of 16 adult-dose piglets. Four hours postresuscitation, pediatric dosing resulted in fewer elevations of cardiac troponin T (0 of 12 piglets vs. 6 of 11 piglets, $p = 0.005$) and less depression of left ventricular ejection fraction ($p < 0.05$). Most importantly, more piglets survived to 24 h with good neurologic scores after pediatric shocks than adult shocks (13 of 16 piglets vs. 4 of 16 piglets, $p = 0.004$).

CONCLUSIONS In this model, pediatric shocks resulted in superior outcome compared with adult shocks. These data suggest that adult defibrillation dosing may be harmful to pediatric patients with VF and support the use of attenuating electrodes with adult biphasic AEDs to defibrillate children. (J Am Coll Cardiol 2005;45:786–9) © 2005 by the American College of Cardiology Foundation

Automated external defibrillators (AEDs) designed for adults are typically the first defibrillators available for prehospital cardiac arrests. Recognizing that some adult AEDs have automated diagnostic algorithms that are accurate in children, AEDs are now recommended for children one to eight years of age (1). However, a specific pediatric AED dose is not stipulated. Notably, the standard weight-based dosing strategy for pediatric defibrillation is not easily implemented in AEDs (2). Technologic developments have enabled the delivery of a pediatric dose by attenuating the adult defibrillation dose with pediatric pads/cable systems, thereby delivering 50 to 86 J rather than 150 to 360 J (3,4).

This attenuated dosing strategy is effective in piglet models of ventricular fibrillation (VF) (3–5). We have previously established that a pediatric defibrillation dosing strategy using attenuated adult biphasic shocks was at least as safe and effective as standard weight-based monophasic dosing in a swine model of prehospital pediatric VF (4). We hypothesized that biphasic pediatric defibrillation dosing and escalating biphasic adult dosing would be equally effective at terminating pediatric VF, but that the adult shocks would result in greater postresuscitation myocardial dysfunction.

MATERIALS AND METHODS

Animal preparation. Protocols were approved by the University of Arizona Institutional Animal Care and Use Committee. Thirty-two female piglets were endotracheally intubated and anesthetized with 1% to 2.5% isoflurane in room air. The approximately two-month-old piglets (~20 kg) were chosen because they were older than neonates and younger than adolescents, and their transthoracic impedance was similar to those of one- to eight-year old children. Ventilation was delivered by a volume-regulated time-cycled ventilator (Narkomed 2A, North American Drager, Dräger Medical, Inc., Telford, Pennsylvania), adjusted to maintain end-tidal carbon dioxide at 40 ± 4 mm Hg.

Micromanometer-tipped catheters (MPC-500, Millar Instruments, Houston, Texas) were placed in the right atrium, left ventricle (LV), and aorta. A pacing catheter electrode was placed temporarily into the right ventricle to induce VF. Correct catheter placement was verified by

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Abbreviations and Acronyms

AED = automated external defibrillator
CPR = cardiopulmonary resuscitation
cTnT = cardiac troponin T
LV = left ventricle
LVEF = left ventricular ejection fraction
ROSC = return of spontaneous circulation
VF = ventricular fibrillation

fluoroscopy. Adhesive defibrillation electrodes were placed in right parasternal and left dorsolateral positions.

Measurements. Electrocardiograms and aortic, atrial, and LV pressures were recorded continuously (P3P Ponemah Physiology Platform, Gould Instrument Systems, Charlotte, North Carolina). Left ventriculograms were recorded in normal sinus rhythm at baseline and 1 and 4 h postresuscitation to calculate left ventricular ejection fraction (LVEF) (4,6). Two observers evaluated neurologic function 24 h after resuscitation using the swine Cerebral Performance Category score (4). Cardiac troponin T (cTnT) levels were assessed 4 h after resuscitation (CARDIAC reader, Roche Diagnostics, Indianapolis, Indiana); cTnT concentration <0.05 ng/ml is negative, ≥ 0.1 ng/ml is positive, and >2.0 ng/ml indicates massive myocardial damage.

Voltage and current waveforms for shocks were recorded by a digital oscilloscope (Model TDS5054, Tektronix, Inc., Beaverton, Oregon) to assess defibrillation waveform characteristics and transthoracic impedance. Pre- and postshock electrocardiographic waveforms were recorded (LIFEPAK 12 Defibrillator/Monitor and CODE-STAT Suite Data Management System, Medtronic, Emergency Response Systems, Inc., Redmond, Washington) for later evaluation. Termination of VF was determined 10 s postshock.

Experimental protocol. After baseline data collection, VF was induced with 100-Hz alternating current, and confirmed by electrocardiographic waveform and precipitous decline in aortic pressure. Ventilation was discontinued. After 7 min of untreated VF, piglets were randomized to adult or pediatric dose shocks (1 to 3 shocks, as needed). If VF persisted, or if aortic pressure was <50 mm Hg, manual chest compressions were provided at a metronome-guided rate of 100 compressions/min and mechanical ventilation at 12 breaths/min with 100% oxygen. Shocks and cardiopulmonary resuscitation (CPR) were provided until return of spontaneous circulation (ROSC), defined as an aortic peak systolic pressure of >50 mm Hg and a pulse pressure of >20 mm Hg for >1 min. Epinephrine (0.02 mg/kg) was administered intravenously if ROSC was not attained within 20 min, mimicking typical timing of drug delivery for prehospital cardiac arrest (4). Epinephrine doses were repeated at 3-min intervals during continued CPR. If ROSC was not attained by 27 min after VF induction, resuscitation was terminated. When ROSC was attained, the animals were monitored for a 4-h intensive care period and observed up to 24 h.

Treatment groups. The adult biphasic experimental group received biphasic truncated exponential waveform shocks (ADAPTIV Biphasic LIFEPAK 12 Defibrillator/Monitor, Medtronic) set to deliver 200/300/360 J via standard adult-sized pads (111 cm^2 conductive area). The pediatric dosage group received shocks from the same defibrillator using the same energy settings, but delivered through prototype infant/child reduced energy defibrillation electrodes (52 cm^2 conductive area, Medtronic), which reduced the nominal delivered energy to 50/75/86 J.

Data analysis. Discrete variables were compared with Fisher exact test and continuous variables by unpaired Student *t* test and described as mean ± SEM (Statview 5.0). Longitudinal data were analyzed using a repeated measures analysis of variance (4).

RESULTS

The 32 piglets (19 ± 1 kg) were one to three months old. The two treatment groups did not differ in baseline parameters (Table 1).

By design, the highest energy delivered was lower for pediatric (74 ± 3 J) than adult shocks (259 ± 16 J), $p <$ 0.05. Similarly, the largest delivered peak current was lower

Table 1. Data at Baseline and 1 h Postresuscitation

	Baseline		1-h Postresuscitation	
	Pediatric	Adult	Pediatric	Adult
n	16	16	14	14
Weight (kg)	19.1 ± 1.2	18.2 ± 1	—	—
Heart rate (beats/min)	112 ± 5	119 ± 1	125 ± 5*	150 ± 7
AoS (mm Hg)	71 ± 3	70 ± 3	66 ± 2	71 ± 3
AoD (mm Hg)	46 ± 2	46 ± 2	45 ± 1	48 ± 2
RAP (mm Hg)	7 ± 1	6 ± 1	9 ± 1	8 ± 1
LVEDP (mm Hg)	10 ± 1	11 ± 1	13 ± 1	14 ± 2
Tau (μ)	34 ± 4	38 ± 2	46 ± 4	46 ± 5
pHa	7.46 ± 0.01	7.47 ± 0.01	—	—
P_aO_2 (mm Hg)	96 ± 3	89 ± 6	—	—

*Pediatric differs from adult, $p = 0.006$. Mean ± SEM.

AoD = aortic diastolic pressure; AoS = aortic systolic pressure; LVEDP = left ventricular end-diastolic pressure; P_aO_2 = arterial partial pressure of oxygen; pHa = arterial pH; RAP = right atrial pressure.

Table 2. Shock Characteristics

	Pediatric	Adult
Total shocks delivered	4.8 ± 1.2	2.6 ± 1
Largest delivered peak current (A)	12.9 ± 0.3*	38.1 ± 1.6
Largest delivered energy (J)	74 ± 3*	259 ± 16
Cumulative delivered energy (J)	346 ± 92	721 ± 351
Impedance (Ω)	68 ± 2†	38 ± 1

Pediatric differs from adult. *$p < 0.05$ and †$p < 0.001$. Mean ± SEM.

with pediatric shocks (12.9 ± 0.3 A vs. 38.1 ± 1.6 A, $p < 0.05$). Transthoracic impedance is inversely related to pad size and shock intensity; therefore, the impedance measured was lower for adult shocks (38.3 ± 0.9 Ω) than pediatric shocks (67.6 ± 2.0 Ω), $p < 0.001$ (Table 2).

The pediatric dose was less effective at initially terminating VF; 4 of 16 versus 12 of 16 piglets had termination of VF with the first shock ($p = 0.01$) and 11 of 16 versus 16 of 16 with the first 2 shocks (Fig. 1). Shock-refractory VF occurred in two piglets; one pediatric dose animal never had termination of VF and one adult dose animal had persistent VF after refibrillation. Total duration of CPR (3.4 ± 1.1 min vs. 2.7 ± 0.8 min, $p = 0.3$) and time elapsed before ROSC (11.1 ± 1.1 min vs. 9.9 ± 0.8 min, $p = 0.3$) did not differ.

Fifteen of 16 pediatric-dose piglets attained ROSC, as did 14 of 16 adult-dose piglets. Twenty-four-hour survival tended to occur more often after pediatric shocks (13 of 16 vs. 8 of 16, $p = 0.14$). Most importantly, 24-h survival with good neurologic outcome was superior after pediatric shocks (13 of 16 vs. 4 of 16, $p = 0.004$) (Fig. 1).

The LVEF decreased relative to baseline at 1 h postresuscitation in both groups ($p < 0.05$) (Fig. 2). At 1 and 4 h postresuscitation, the LVEF decreased less after pediatric than adult doses ($p < 0.05$). In addition, heart rate was lower after pediatric than adult shocks 1 h postresuscitation (125 ± 5 beats/min vs. 150 ± 7 beats/min, $p = 0.006$) and tended to be lower 4 h postresuscitation (108 ± 3 beats/min vs. 121± 7 beats/min, $p = 0.08$).

The cTnT levels were uniformly undetectable at baseline.

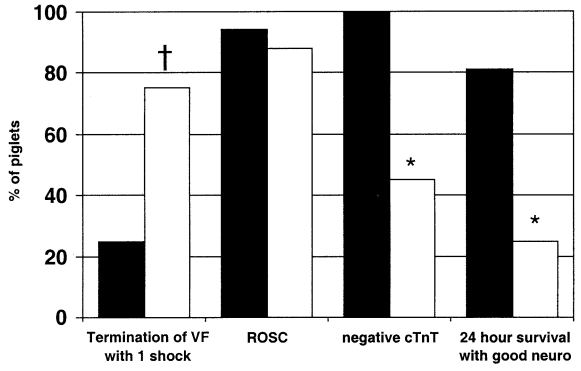

Figure 1. Resuscitation outcomes of piglets receiving pediatric **(black bars)** versus adult **(white bars)** defibrillation shocks. ROSC = return of spontaneous circulation; VF = ventricular fibrillation; neuro = neurologic outcome; cTnT = cardiac troponin T, negative cTnT refers to undetectable cTnT 4 h postresuscitation. *$p < 0.005$; †$p = 0.01$.

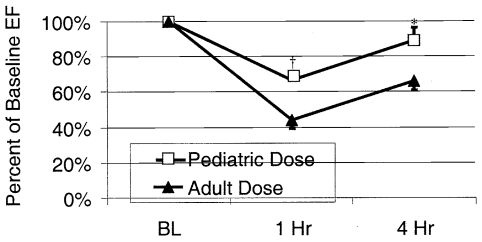

Figure 2. Changes in left-ventricular ejection fraction (EF) from preventricular fibrillation baseline (BL) to 1 and 4 h postresuscitation. Mean ± SEM.*$p < 0.05$, †$p < 0.01$.

None of 12 piglets had elevated cTnT levels after pediatric shocks, compared with 6 of 11 piglets after adult shocks, $p = 0.005$. Five of the six cTnT elevations were 0.1 to 0.2 ng/ml; one was 0.29 ng/ml.

DISCUSSION

This study establishes that a pediatric dosing strategy can result in superior 24-h survival with good neurologic outcome compared with adult dosing in an animal model of prolonged pediatric VF. The pediatric dosage was associated with less myocardial damage, on the basis of the absence of elevated cTnT levels, and less postresuscitation myocardial dysfunction.

The adult-shock group was treated differently in two ways: higher shock dose and larger electrode size. The combination resulted in substantially higher peak current delivery (Table 2). Postresuscitation myocardial dysfunction is typically more pronounced after longer periods of untreated VF and more prolonged duration of CPR (7). However, in this study the two groups did not differ in regard to duration of untreated VF, duration of CPR, or time to ROSC. Therefore, the myocardial damage was presumably mediated by the high peak current delivery.

Several animal studies have examined cardiac injury and dysfunction following defibrillation. Babbs et al. (8) demonstrated that monophasic defibrillation doses >10 J/kg caused myocardial damage in ~25% of adult dogs. Gaba and Talner (9) established that myocardial damage occurred with cumulative doses >150 J/kg when applying monophasic shocks of 20 to 40 J to neonatal piglets weighing <5 kg. Killingsworth et al. (10) documented transient dose-dependent postdefibrillation LV dysfunction in piglets after brief-duration VF, yet were impressed by the high resiliency of myocardial function after biphasic defibrillation dosages reaching 100 J/kg. These studies support our findings that high defibrillation dosages can be detrimental to immature (pediatric) myocardium; however, they did not evaluate survival or neurologic status after adult versus pediatric shocks in immature animals.

The recommended monophasic 2 J/kg defibrillation dose for children is based on animal studies of short-duration VF and a single retrospective study of in-hospital (short-duration) VF by Gutgesell et al. (2). They reviewed 71 transthoracic defibrillation attempts in 27 children and

found that 52 of 57 (91%) monophasic shocks of ~2 J/kg successfully terminated VF. More recent information indicates that biphasic energy waveforms are more efficacious and less toxic than monophasic waveforms in the treatment of VF (11).

We and others (3–5) have demonstrated the safety and effectiveness of a pediatric dosing strategy using biphasic shocks of 50 to 86 J for the treatment of prolonged VF in piglet models. We randomized 3.4 to 27 kg piglets to treatment with pediatric doses of either monophasic 2/4/4 J/kg shocks or the same biphasic attenuated adult shock dosage used in the present study (50/75/86 J). The biphasic attenuated shocks were at least as safe and effective for the smaller piglets and substantially superior for the larger piglets. In the largest piglets (24-kg group), biphasic attenuated shocks resulted in more effective termination of VF, less postresuscitation myocardial dysfunction, and a higher rate of 24-h survival with good neurologic outcome.

Study limitations. Although this experiment was not blinded, piglets were randomly assigned to a defibrillation dose, and the resuscitation and postresuscitation protocols were standardized and strictly followed. The neurologic evaluations using the swine Cerebral Performance Categories were not blinded, but one of the observers was an experienced board-certified veterinarian, and the outcome measures are not subtle or easily manipulable. Piglets with good outcomes can walk, eat, and respond relatively normally to their environment, whereas those with poor outcomes have gross neurologic deficits (respond sluggishly to visual, auditory, and other stimuli, and are unable to walk or feed themselves). Because postresuscitation myocardial function was an important intermediate outcome measure, we did not provide postresuscitation hemodynamic support. It is possible that aggressive postresuscitation care could have improved the 24-h survival and neurologic outcome.

There are little data to support or refute the applicability of our piglet results to children. Gurnett and Atkins reported a three-year-old child who, after receiving a biphasic shock of 150 J (9 J/kg), had no elevations of serum creatine kinase or cardiac troponin I and normal postresuscitation ventricular function on echocardiogram (12). Similarly, approximately one-half of our animals had normal cTnT levels after adult shocks. Importantly, postresuscitation myocardial damage with elevated cardiac enzymes and poor ventricular function is well documented after pediatric cardiac arrests (13).

Conclusions. In summary, both pediatric and adult doses effectively terminated VF in this piglet model of prehospital VF, but the pediatric doses resulted in less myocardial damage and better 24-h outcomes. Our findings suggest that adult defibrillation doses may be harmful for children. Although human data are certainly needed, these animal data support the new pediatric AED guidelines: "Ideally, the device should deliver a pediatric dose" (1).

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